

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference OMFR143	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 95/08331	International filing date (day/month/year) 30/06/95	(Earliest) Priority Date (day/month/year) 30/06/94
Applicant OKLAHOMA MEDICAL RESEARCH FOUNDATION et al.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ Certain claims were found unsearchable (see Box I).
2. ☐ Unity of invention is lacking (see Box II).
3. ☐ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
 - ☐ filed with the international application.
 - ☐ furnished by the applicant separately from the international application,
 - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
 - ☐ Transcribed by this Authority
4. With regard to the title, ☒ the text is approved as submitted by the applicant.
 - ☐ the text has been established by this Authority to read as follows:
5. With regard to the abstract,
 - ☒ the text is approved as submitted by the applicant.
 - ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:
 - Figure No. ☐ as suggested by the applicant.
 - ☐ because the applicant failed to suggest a figure.
 - ☐ because this figure better characterizes the invention.
 - ☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 95/08331

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 G01N33/92 C07K16/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 G01N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 407 035 (LUCA NICOLAE DR) 9 January 1991 see claims 1-4 ---	1-3,6,7
X	EP,A,0 257 778 (SCRIPPS CLINIC RES) 2 March 1988 see the whole document ---	1-3,13,14
A	WO,A,86 05493 (SCRIPPS CLINIC RES) 25 September 1986 ---	
A	WO,A,93 07165 (SCRIPPS RESEARCH INST) 15 April 1993 ---	
A	WO,A,93 18067 (ABBOTT LAB) 16 September 1993 cited in the application ---	
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

23 October 1995

Date of mailing of the international search report

15. 11. 95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
 Fax (+ 31-70) 340-3016

Authorized officer

Cartagena y Abella,P

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BIOCHIMICA ET BIOPHYSICA ACTA, vol. 876, 1986 pages 91-100, E. KOREN ET AL. 'Characterization of a monoclonal antibody that binds equally to all apolipoprotein and lipoprotein forms of human plasma apolipoprotein B. I. Specificity and binding studies.' cited in the application ---	
A	BIOCHIMICA ET BIOPHYSICA ACTA, vol. 876, no. 1, 21 March 1986 pages 101-107, E. KOREN ET AL. 'Characterization of a monoclonal antibody that binds equally to all apolipoprotein and lipoprotein forms of human plasma apolipoprotein B.' cited in the application ---	
A	ARTERIOSCLEROSIS, vol. 6, no. 5, September 1986 page 521a E. KOREN ET AL. 'Use of "Pan" monoclonal antibody for quantification of apolipoprotein A-II.' cited in the application ---	
A	ATHEROSCLEROSIS, vol. 95, 1992 pages 157-170, E. KOREN ET AL. 'Apolipoprotein A-I and apolipoprotein B containing lipoprotein particles in coronary patients treated with extracorporeal low density lipoprotein precipitation.' cited in the application -----	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 95/08331

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0407035	09-01-91	US-A- 5187068	16-02-93
EP-A-0257778	02-03-88	AT-T- 120233	15-04-95
		AU-B- 7657387	11-02-88
		DE-D- 3751182	27-04-95
		ES-T- 2070820	16-06-95
		FI-B- 92714	15-09-94
		JP-A- 63279783	16-11-88
		US-A- 5330910	19-07-94
WO-A-8605493	25-09-86	US-A- 4677057	30-06-87
		AU-B- 596096	26-04-90
		AU-B- 5627286	13-10-86
		EP-A- 0218630	22-04-87
		JP-T- 62502705	15-10-87
WO-A-9307165	15-04-93	US-A- 5408038	18-04-95
WO-A-9318067	16-09-93	NONE	

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Washington D.C. 20231
United States of America

in its capacity as elected Office

Date of mailing (day/month/year) 04 March 1996 (04.03.96)	
International application No. PCT/US95/08331	Applicant's or agent's file reference OMRF143
International filing date (day/month/year) 30 June 1995 (30.06.95)	Priority date (day/month/year) 30 June 1994 (30.06.94)
Applicant KOREN, Eugen et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

26 January 1996 (26.01.96)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

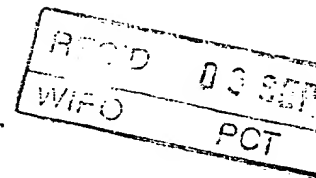
Martine Lee

Telephone No.: (41-22) 730.91.11

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)


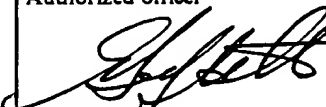


Applicant's or agent's file reference OMFR143	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/ US 95/ 08331	International filing date (day/month/year) 30/06/1995	Priority date (day/month/year) 30/06/1994
International Patent Classification (IPC) or national classification and IPC G01N33/92		
Applicant OKLAHOMA MEDICAL RESEARCH FOUNDATION et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This **REPORT** consists of a total of 8 sheets, including this cover sheet.
- ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consists of a total of 11 sheets.

3. This report contains indications and corresponding pages relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 26/01/1996	Date of completion of this report 05.09.96
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer  E. Luzzatto Telephone No.

I. Basis of the report

1. This report has been drawn up on the basis of (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):

☐ the international application as originally filed.

☒ the description, pages 1-74 _____, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____.

☒ the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 1-44 _____, filed with the letter of 30/06/96,
Nos. _____, filed with the letter of _____.

☐ the drawings, sheets/fig _____, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____.
☐ the claims, Nos. _____.
☐ the drawings, sheets/fig _____.

3. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

- 1) The fact that the antibody reactive with a specific lipoprotein or apolipoprotein binds to a stable, conformation independent epitope which is uninfluenced by

the lipid content (amendments to claims 1, 18, 31, 32, 35) is not disclosed in the application as originally filed. The application apparently only discloses such a feature in respect of anti-LDL antibodies (see p. 26, l. 20-32). With respect to other lipoproteins or apolipoproteins the application only refers to the specificity of the antibodies.

For instance, antibody HB₃CB₃ binds LDL and not VLDL: according to the description this may be due to the fact that the epitope recognised by it may be conformationally changed or masked by lipids in VLDL (see p. 27, l. 25-28).

Thus, it is clear that it is an epitope of LDL which has to be uninfluenced by the lipid content.

- 2) The amendment to claims 13, 15-17 are not supported by the application as originally filed since it never mentions the possibility of adding non-immobilised antibodies.

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 4,5,8,9,12,15-17,19,21,22,24,25,28-30,35-41,43, 44 YES
	Claims 1-3,6,7,10,11,13,14,18,20,23,26,27,31-34,42 ____ NO
Inventive Step (IS)	Claims 4,5,15-17,21,22,28-30,35-40,43 ____ YES
	Claims 1-3,6-14,18-20,23-27,31-34,41,42,44 ____ NO
Industrial Applicability (IA)	Claims 1-44 ____ YES
	Claims ____ NO

2. CITATIONS AND EXPLANATIONS

The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of claims 1-3,6,7,10,11,13,14,18,20,23,26,27,31-34 and 42 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).

EP-A-257778 (D1) discloses monoclonal antibodies against apoprotein B-100 and methods for its detection, such as solid-phase assays, which comprise their use (see p. 3, l. 40-p. 5, l. 25, p. 9, l. 28-38, p. 10, l. 32-34, p. 12, l. 25-p. 15, l. 12 and claims).

EP-A-407035 (D2) discloses assays comprising the use of specific anti-apoprotein antibodies and of an agent which stains the lipid fraction of lipoproteins (see col. 7, l. 13-col. 11, l. 11, col. 17, l. 43-45 and claims 1-4). Although D2 does not provide any examples of antibodies which could be used, it appears clearly that the skilled person, at least in the opinion of the authors of D2, would have had no difficulties in finding the suitable reagents for the claimed assays.

That this is indeed the case is shown by D1 and by the

other documents cited in the International Search Report. WO-A-8605493, for instance, discloses specific anti-apoprotein A monoclonal antibodies and their use. Also WO-A-9307165 discloses monoclonal antibodies specific for LDL and HDL and methods to determine their relative ratio which comprise the use of the said antibodies (see claims).

- 2) Dependent claims 8, 9, 12, 19, 24, 25, 41 and 44 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, involve an inventive step since they appear commonplace in the art.
- 3) On the other hand, the subject-matter of claims 4, 5, 15, 16, 17, 21, 22, 28-30, 35-40 and 43 appears to meet the requirements of Art. 33 PCT.
 - 3.1) The subject-matter of claim 35 is broad but, in view of the available prior art and interpreted in the light of the description (p. 26-27), appears to be novel and inventive (see however point VIII of this Opinion).
The same applies to claims 38 and 39.
 - 3.2) The subject-matter of claims 4, 5, 21, 22, 36, 37 and 40 is novel and, in the light of its higher specificity of the claimed monoclonal antibody compared to the antibodies of the prior art, appears also to be inventive.
 - 3.3) The methods to which claims 15-17 relate are based on antibodies known from the prior art; however, the skilled person would not have found in the prior art any clear-cut indication which could have lead him/her to the claimed methods which comprise the combined use of the said antibodies for the determination of the relative ratios of various lipoproteins (see however point VIII of the present Opinion).

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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The same reasoning supports the novelty and the inventiveness of the subject-matter of claims 28-30.

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

- 1) A receipt of the deposit of the claimed hybridomas will be necessary in some cases when entering the national or regional phase. The EPO, for instance, will require the filing of the said receipt (see R. 28(1) and (2) EPC and Guidelines for Examination in the EPO, C-II, 6.3)

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

- 1) The application does not meet the requirements of Article 6 PCT because claims 15-17, 28-30 and 35 are not clear.
 - 1.1) Claims 15-17 and 28-30 relate to monoclonal antibodies whose specificity is solely defined on the basis of that of antibodies of the prior art, which is disclosed in the description. Since the said specificity is essential to the invention, it should be explicitly present in the claims (see also Guidelines, C-III, 4.2).
 - 1.2) The prior art discloses anti-LDL antibodies which show a low level of cross-reactivity with other lipoproteins (e.g. WO-A-9318067). Since the present invention lies in the higher specificity of the claimed antibodies, the term "significantly" is not sufficiently precise to allow a clear and unambiguous interpretation of the scope of claim 34. The said term should have therefore been replaced by clearer expressions, e.g. by numerical values.
 - 1.3) Claim 43 should apparently have related to claim 42 instead of claim 41 but it has not been amended.
 - 1.4) Claim 41 refers to a second antibody which is however never mentioned in claims 1 and 12 to which it relates.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 95/08331

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 G01N33/92 C07K16/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 G01N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 407 035 (LUCA NICOLAE DR) 9 January 1991 see claims 1-4 ---	1-3,6,7
X	EP,A,0 257 778 (SCRIPPS CLINIC RES) 2 March 1988 see the whole document ---	1-3,13,14
A	WO,A,86 05493 (SCRIPPS CLINIC RES) 25 September 1986 ---	
A	WO,A,93 07165 (SCRIPPS RESEARCH INST) 15 April 1993 ---	
A	WO,A,93 18067 (ABBOTT LAB) 16 September 1993 cited in the application ---	
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

23 October 1995

Date of mailing of the international search report

15.11.95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Cartagena y Abella,P

INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/US 95/08331

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>BIOCHIMICA ET BIOPHYSICA ACTA, vol. 876, 1986 pages 91-100, E. KOREN ET AL. 'Characterization of a monoclonal antibody that binds equally to all apolipoprotein and lipoprotein forms of human plasma apolipoprotein B. I. Specificity and binding studies.' cited in the application ---</p>	
A	<p>BIOCHIMICA ET BIOPHYSICA ACTA, vol. 876, no. 1, 21 March 1986 pages 101-107, E. KOREN ET AL. 'Characterization of a monoclonal antibody that binds equally to all apolipoprotein and lipoprotein forms of human plasma apolipoprotein B.' cited in the application ---</p>	
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A	<p>ATHEROSCLEROSIS, vol. 95, 1992 pages 157-170, E. KOREN ET AL. 'Apolipoprotein A-I and apolipoprotein B containing lipoprotein particles in coronary patients treated with extracorporeal low density lipoprotein precipitation.' cited in the application -----</p>	

INTERNATIONAL SEARCH REPORT

Original Application No
PCT/US 95/08331

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0407035	09-01-91	US-A- 5187068	16-02-93
EP-A-0257778	02-03-88	AT-T- 120233	15-04-95
		AU-B- 7657387	11-02-88
		DE-D- 3751182	27-04-95
		ES-T- 2070820	16-06-95
		FI-B- 92714	15-09-94
		JP-A- 63279783	16-11-88
		US-A- 5330910	19-07-94
WO-A-8605493	25-09-86	US-A- 4677057	30-06-87
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		AU-B- 5627286	13-10-86
		EP-A- 0218630	22-04-87
		JP-T- 62502705	15-10-87
WO-A-9307165	15-04-93	US-A- 5408038	18-04-95
WO-A-9318067	16-09-93	NONE	